What Approaches are Needed to Advance Proteomic Analysis?

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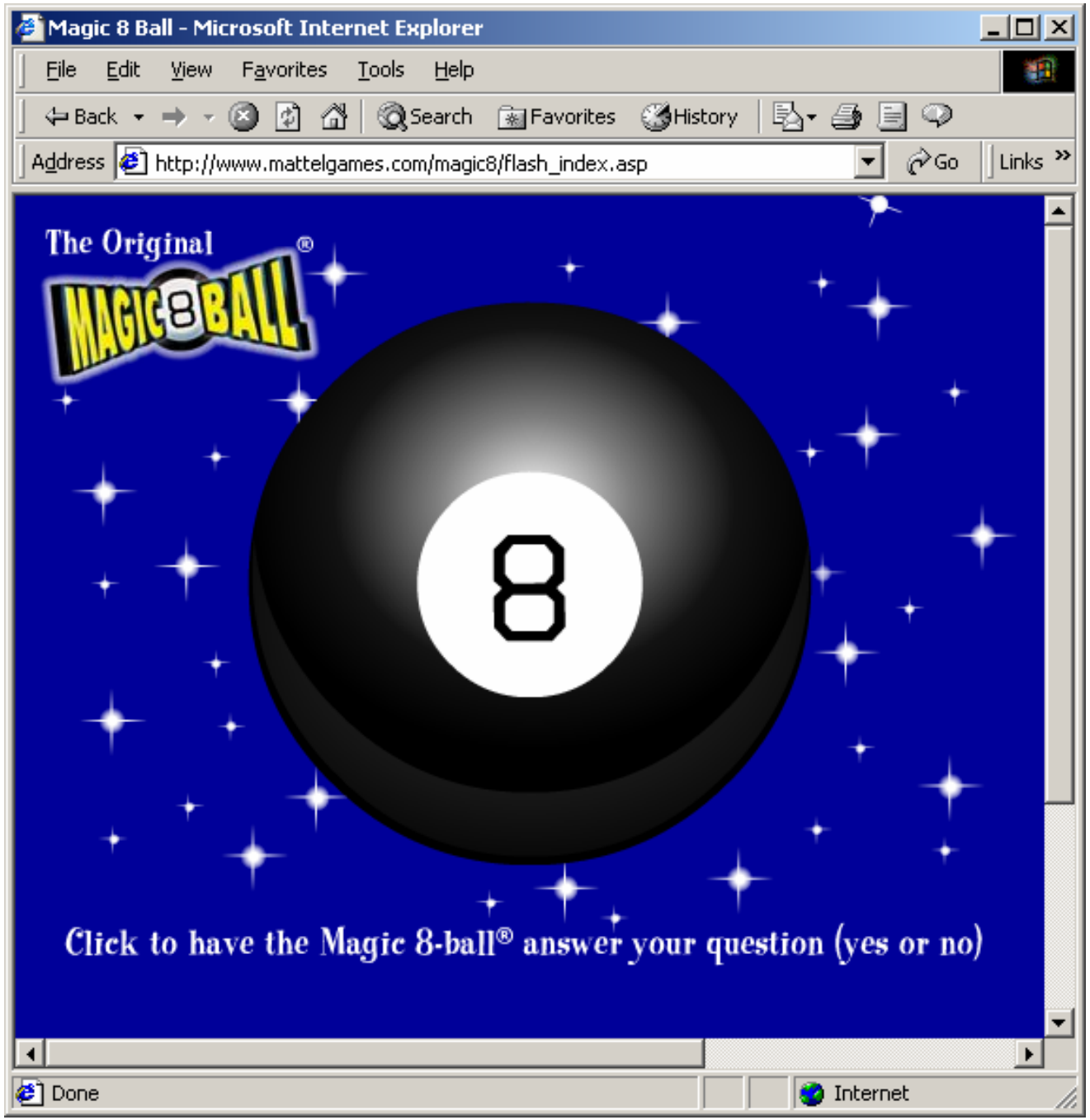
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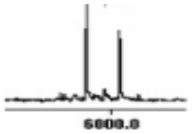
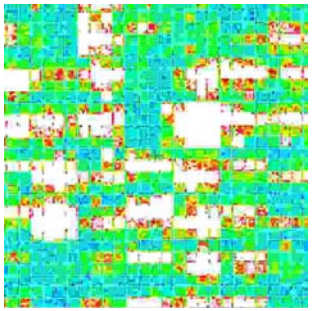
Loosely integrated perspective from:

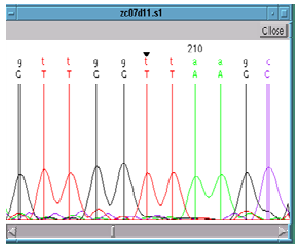
- Fallen population geneticist/biostatistician
- Interloping laboratory scientist
- Non-credentialed bioinformatician

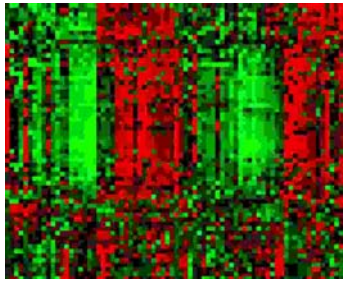
Scarred veteran of the molecular technology revolution …

- Genetics
  - Southern blots
    - RFLPs
    - VNTRs
  - PCR-based
    - STRPs
    - Oligo-based assays
    - Mass spec.
  - Mapping
    - Linkage
    - association
- Genomics
  - Sequencing
    - Silver stained gels
    - Four color sequencing – gel-based
    - Four color sequencing – capillary
  - Transcript profiling
    - SAGE
    - cDNA array
    - Oligo nucleotide









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Lessons learned…

- Initial promise always overstated
  - Innovator's dramatic finding required to break through
  - Insufficient experience with platform
    - known versus unknown demons
  - Disconnect with independent biologic/mechanistic validation

Lessons learned…

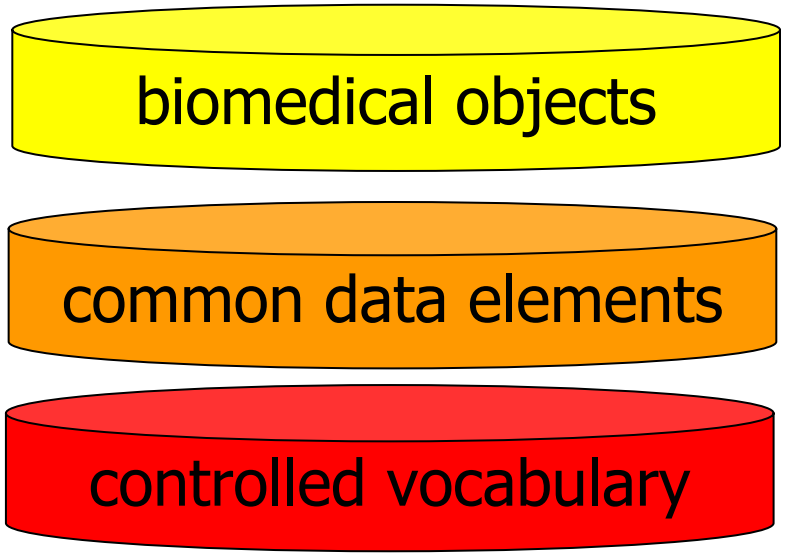
- Open is good!
  - Data sharing
  - Open source code
  - Analytic jamborees

Lessons Learned…

- Standards versus standardization
  - Quality control
    - Experimental protocols
    - Standard external reference
  - Internal controls
  - Standard methodology
  - Data standards
    - Use established standards where they exist
    - Modify/extend existing standards where ever possible
    - Develop new standards "just in time"
  - Standards can NOT be proprietary

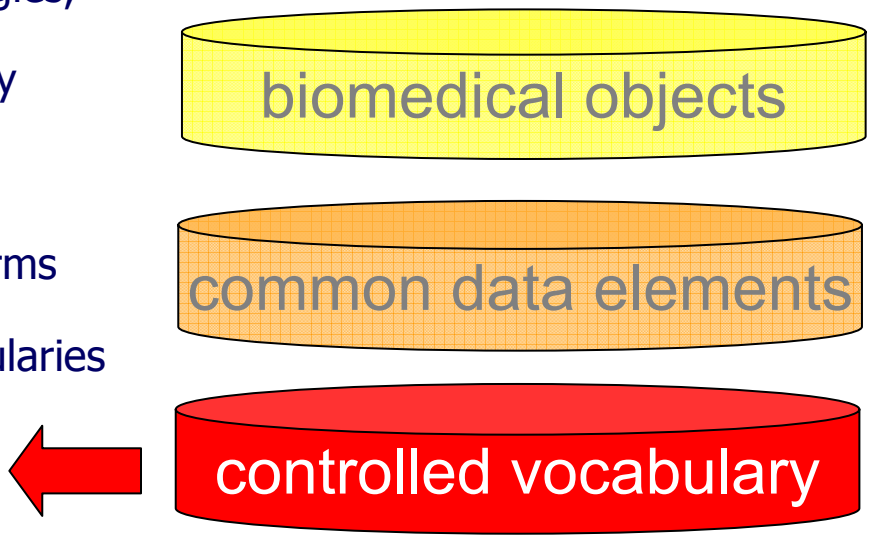
caCORE – common ontologic representation environment

- Information integration
- Cross-discipline reasoning



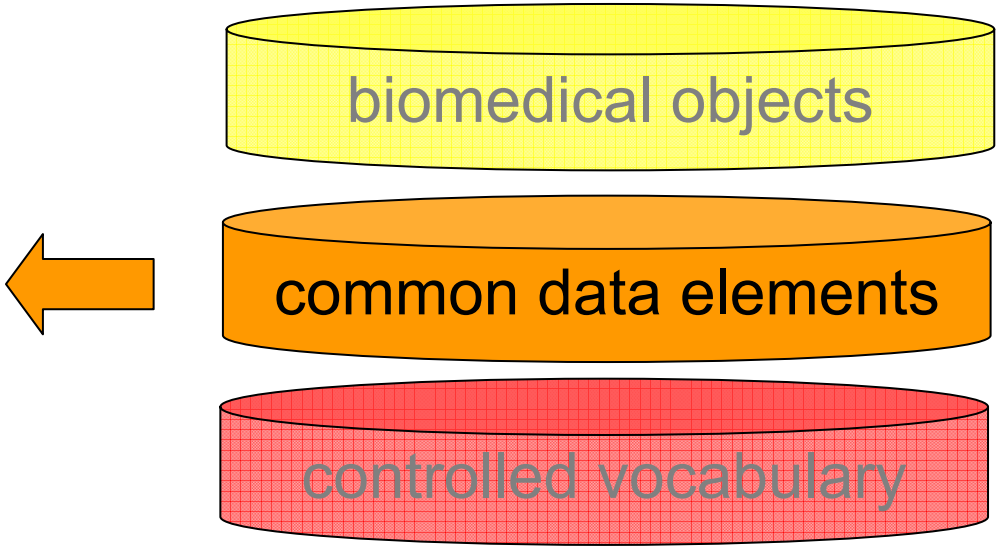
Enterprise Vocabulary

- **NCI Meta-Thesaurus**
  (Cross-map standard vocabularies/ontologies, e.g. SNOMED, MEDRA, ICD)
  - Semantic integration, inter-vocabulary mapping
  - UMLS Metathesaurus extended with cancer-oriented vocabularies
    - 800,000 Concepts, 2,000,000 terms and phrases
    - Mappings among over 50 vocabularies
- **NCI Thesaurus**
  - Description logic-based
  - 18,000 "Concepts"
    - Concept is the semantic unit
    - One or more terms describe a Concept – synonymy
    - Semantic relationships between Concepts



Common Data Elements

- Structured data reporting elements (e.g. LOINC)
- ISO11179 compliant



Lessons Learned…

- Quality measures are transforming
  - Qualitative and quantitative
  - Objective measures critical

Lessons Learned…

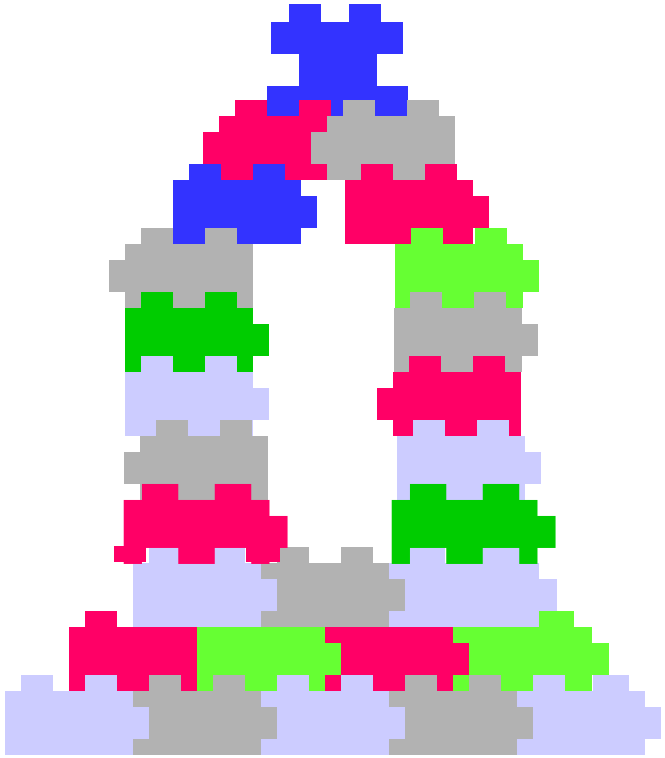
- The devil is in the details
  - Experimental inputs can be as critical as important as outputs
  - Laboratory information management systems (LIMS)

Lessons Learned…

- Today's tools are not likely to be tomorrow's
  - Killer app's
    - Accessible, useful, user friendly apps critical to adoption
    - Not always the best approach (Eisen's cluster analysis)
  - Everything old is new again
    - On the shoulder's of giants…
    - Simpler methods are better
  - Design infrastructure that facilitates rapid exploration of new methods
    - Open source
    - Isolate data from applications
    - Component architecture

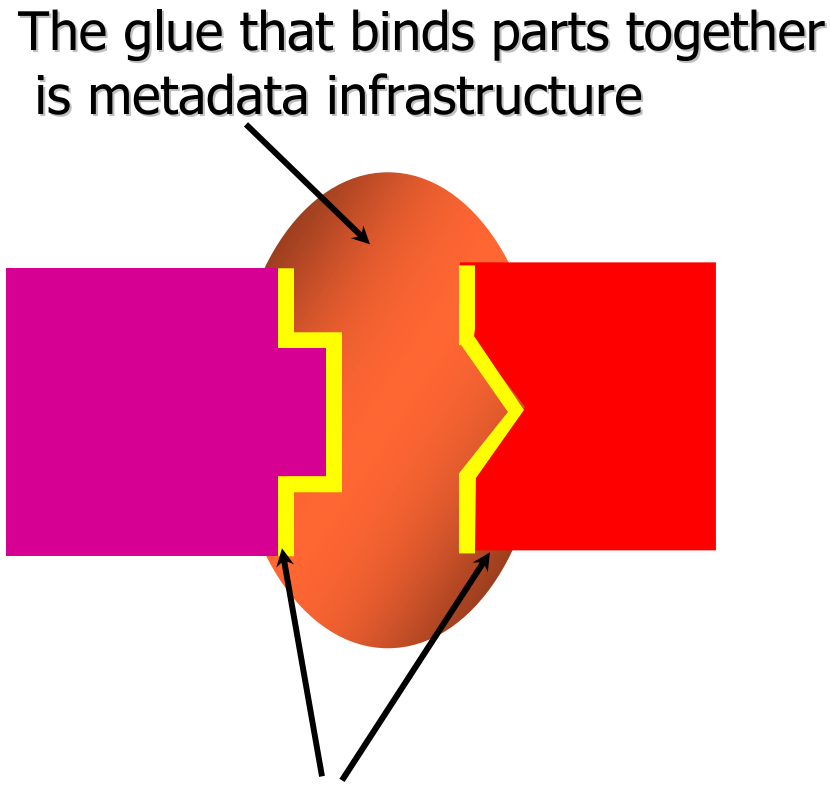
Components: software parts

- Small parts are better for building flexible shapes
- Have a uniform interface medium
- Snap-together connectivity
- Internals can be made from widely varying technologies



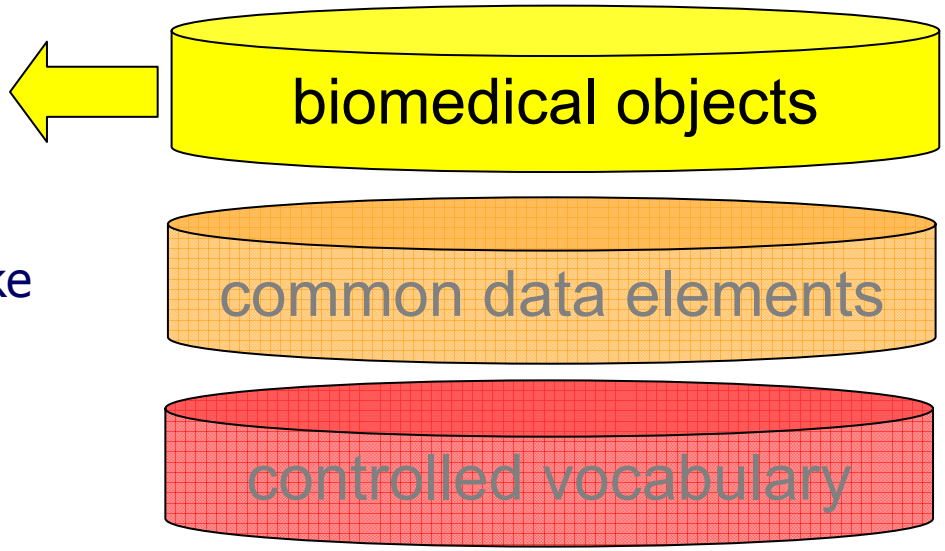
Boundaries and Interfaces

- focus on boundaries, interfaces, how things fit together,
- not on the internal details of how they're built: assume that will be diverse & changing



Biomedical Information Objects

- Computer model of a biomedical object – "Plato's Forms"
  - capture properties of object
  - can be joined together to make complex systems
  - isolate data from data source
  - isolate applications from data
- Examples:
  - HL7-RIM
  - MAGE-OM

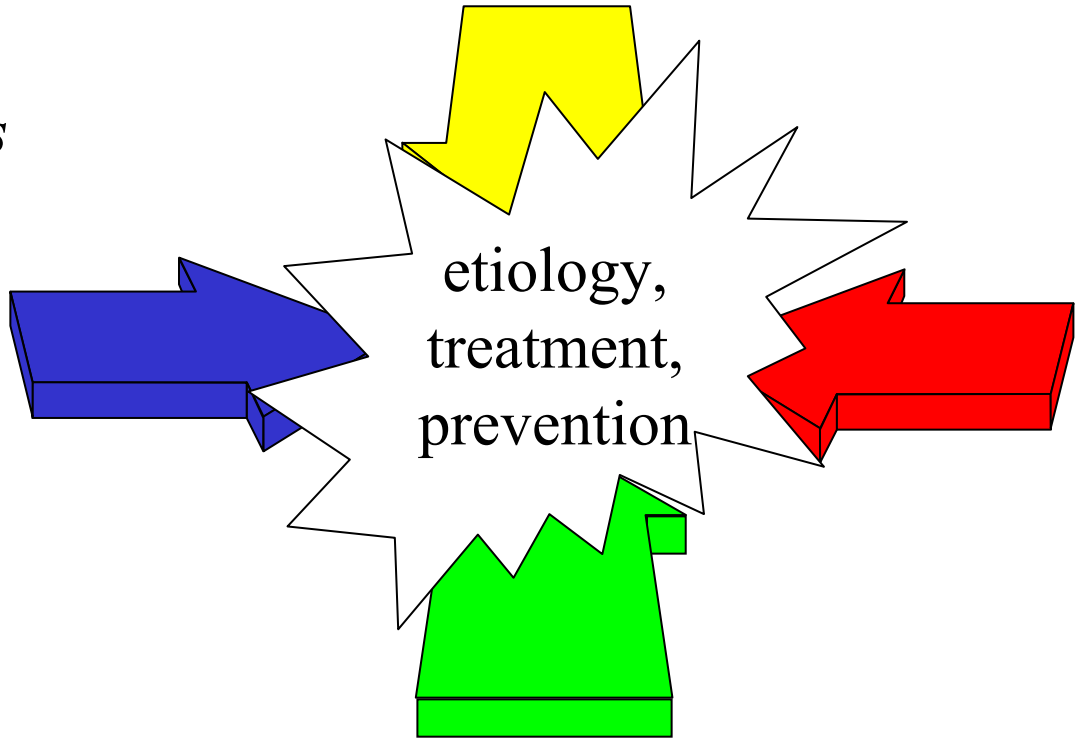


Lessons Learned…

- Study design really does matter
  - New technologies ALWAYS initially appear to reduce the need for rigor
  - Animal models
    - Critical to validation
  - Clinical research considerations
    - Training/testing sets
    - validation sets
    - Over fitting

Lessons Learned…

- You really are going to want to connect these results to other outcomes!
  - Other data types
  - Clinical outcomes



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Pathway Database

- Enhance value of imperfect, but available, pathway knowledge
- Make biological assumptions explicit
- Merge data from separate pathways
- Build a causal framework to support (future) quantitative simulation/analysis

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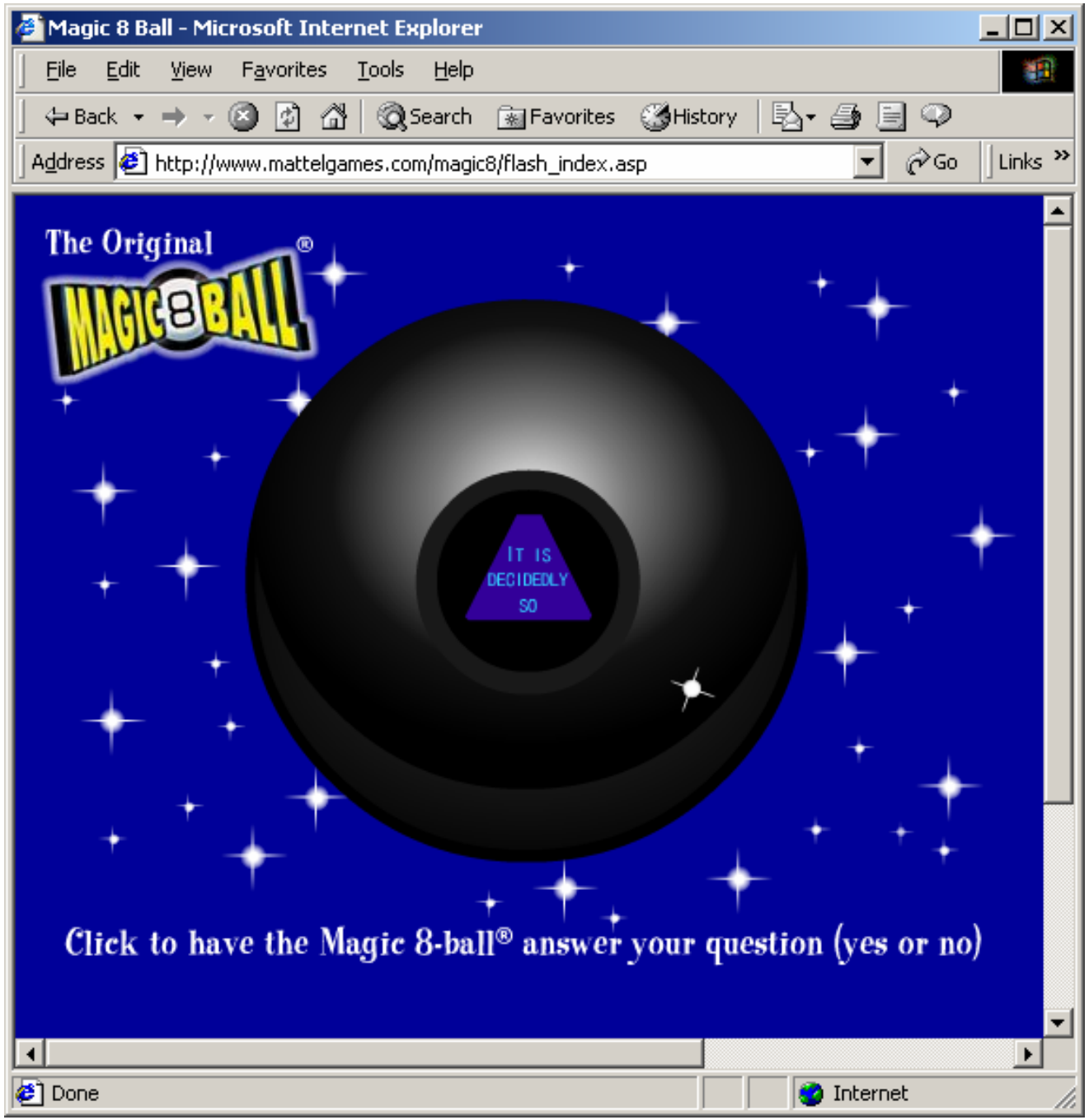
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